
بسم الله
الرحمن
الرحيم

Contrast-induced nephropathy (CIN)

BY

Gamal Fheem, MD

Cardiology Department

Mansoura university

Nephrology MEETING

3 july 2013

Real-life case

- 54 year old male
- Long standing hypertensive
- Renal impairment s cr =3.2 mg/dl
- Class 111 angina pectoris despite OMT
- His son died with RENAL FAILURE
- Refused c angio for time
- Accepted to do

Real-life case

- 12 –h iv hydration 100 ml 0.9 saline
- Procedure

  iso osmlar contrast

  least volume

  C angio

  Svd

  PCI stenting

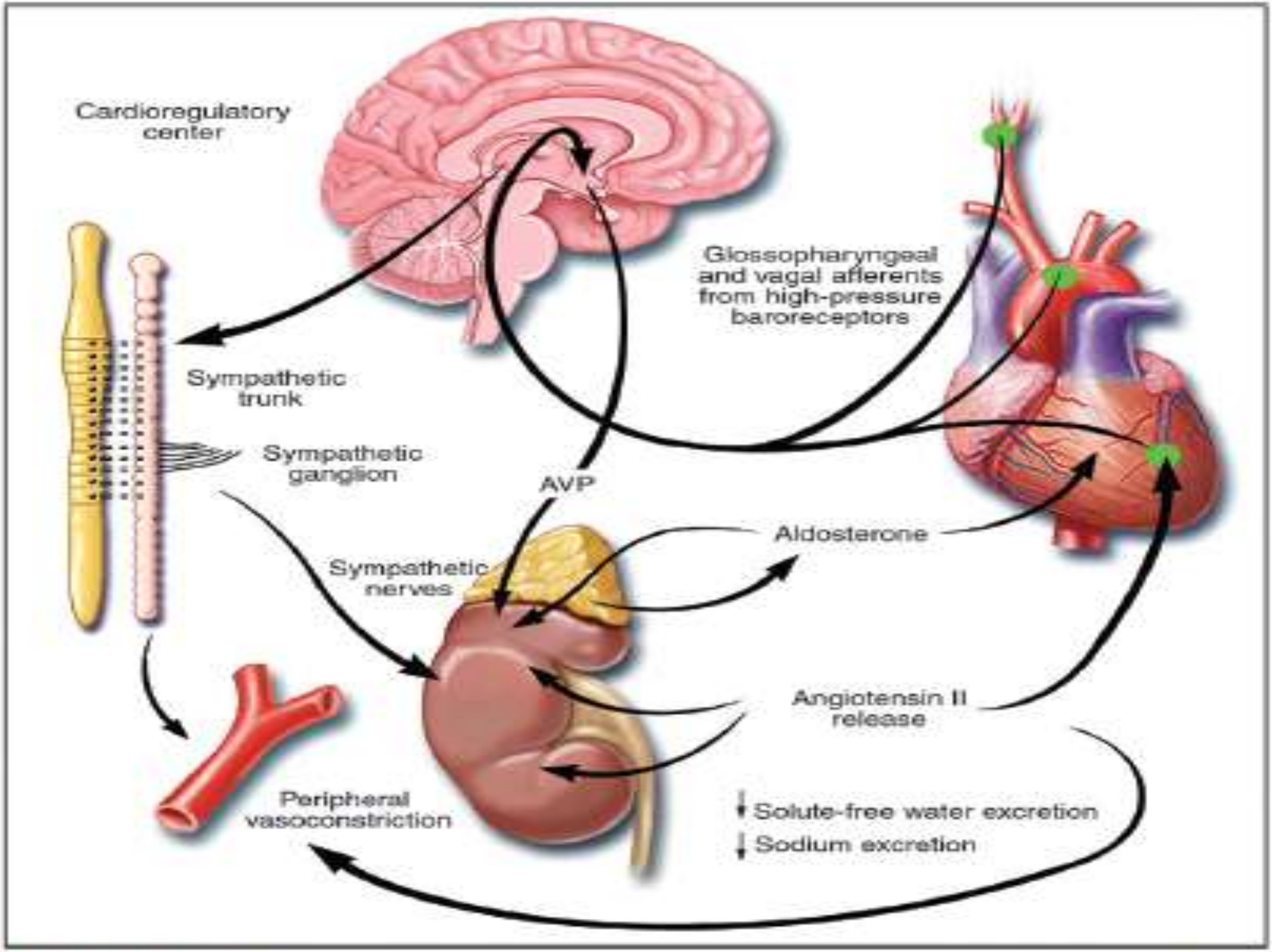
Real-life case

- Post-procedure

  iv hydration

  NAC
- peak s creatinine 4.2 mg 3 days post procedure
- Returned to 3.2 mg/dl at 14 days
- 2-year s creat 3.2 mg/dl

Introduction


Cardioregulatory center
Glossopharyngeal and vagal afferents from high-pressure baroreceptors
Sympathetic trunk
Sympathetic ganglion
AVP
Aldosterone
Sympathetic nerves
Angiotensin II release
Peripheral vasoconstriction
Solute-free water excretion
Sodium excretion

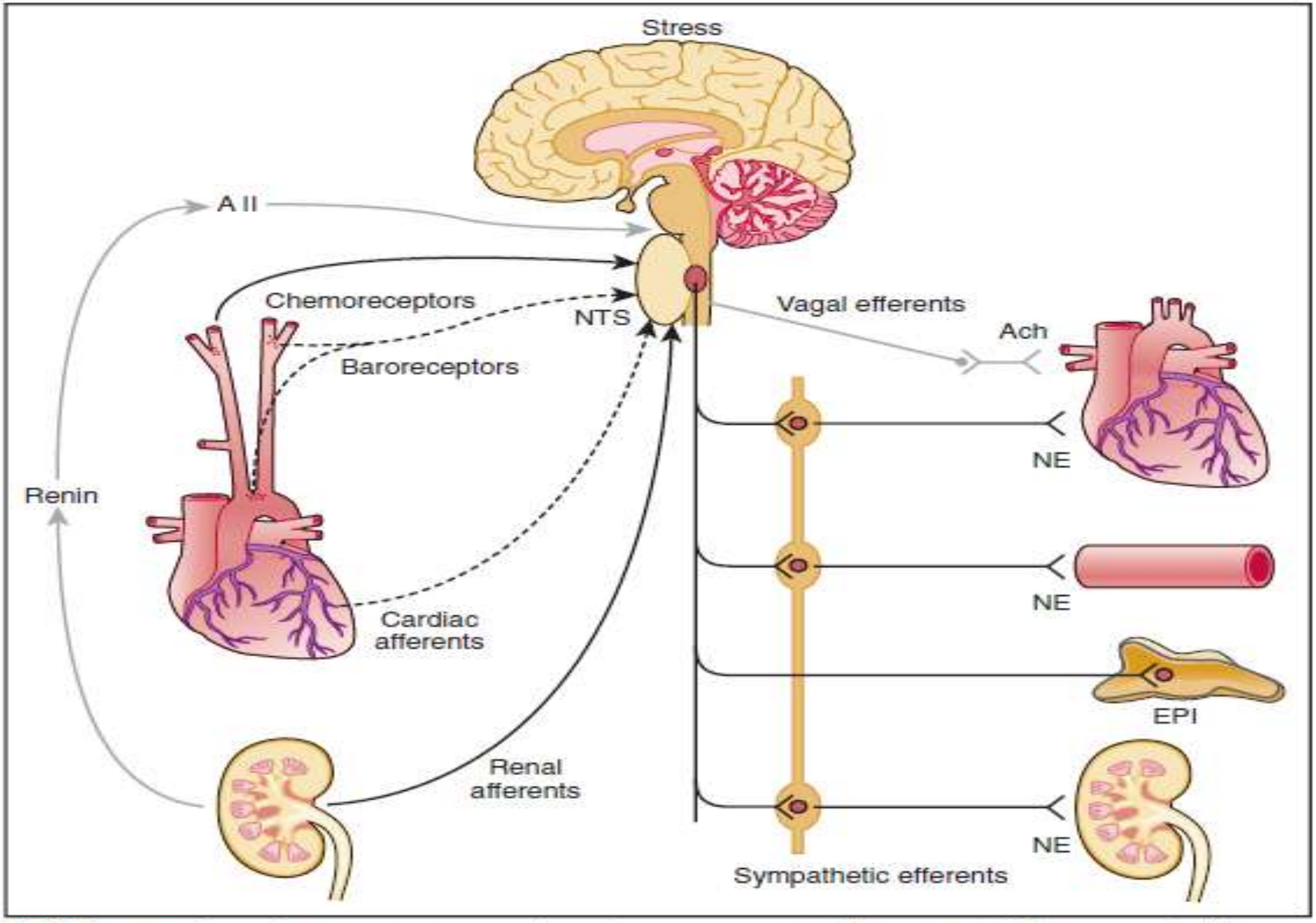


FIGURE 45-5 Sympathetic nervous system. Dotted arrows represent inhibitory neural influences and solid arrows represent excitatory neural influences on sympathetic outflow to the heart, peripheral vasculature, and kidneys. A II = angiotensin II; Ach = acetylcholine; EPI = epinephrine; NE = norepinephrine; NTS = nucleus tractus solitarius.

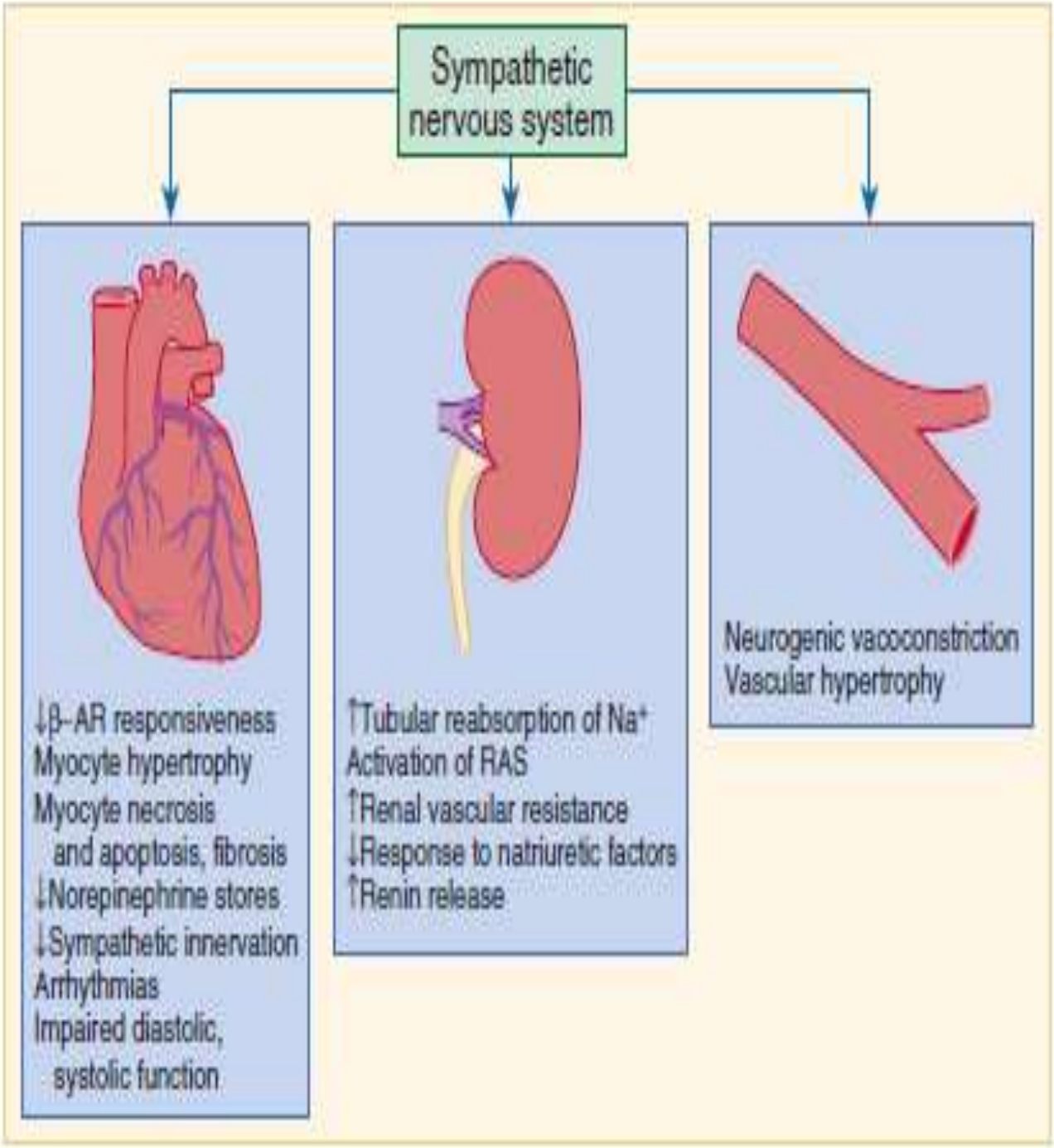


FIGURE 25-2 Activation of the sympathetic nervous system. Increased sympathetic nervous system activity may contribute to the pathophysiologic process of congestive heart failure by multiple mechanisms involving cardiac, renal, and vascular function. In the heart, increased sympathetic nervous system outflow may lead to desensitization of β-adrenergic receptors (β-AR), myocyte hypertrophy, necrosis, apoptosis, and fibrosis. In the kidneys, increased sympathetic activation induces arterial and venous vasoconstriction, activation of the renin-angiotensin system, increase in salt and water retention, and attenuated response to natriuretic factors. In the peripheral vessels, neurogenic vasoconstriction and vascular hypertrophy are induced by increased sympathetic nervous activity. *(From Nohria A, Cusco JA, Creager MA: Neurohormonal, renal and vascular adjustments in heart failure. In Colucci WS [ed]: Atlas of Heart Failure. 4th ed. Philadelphia, Current Medicine, 2005, p 106.)*

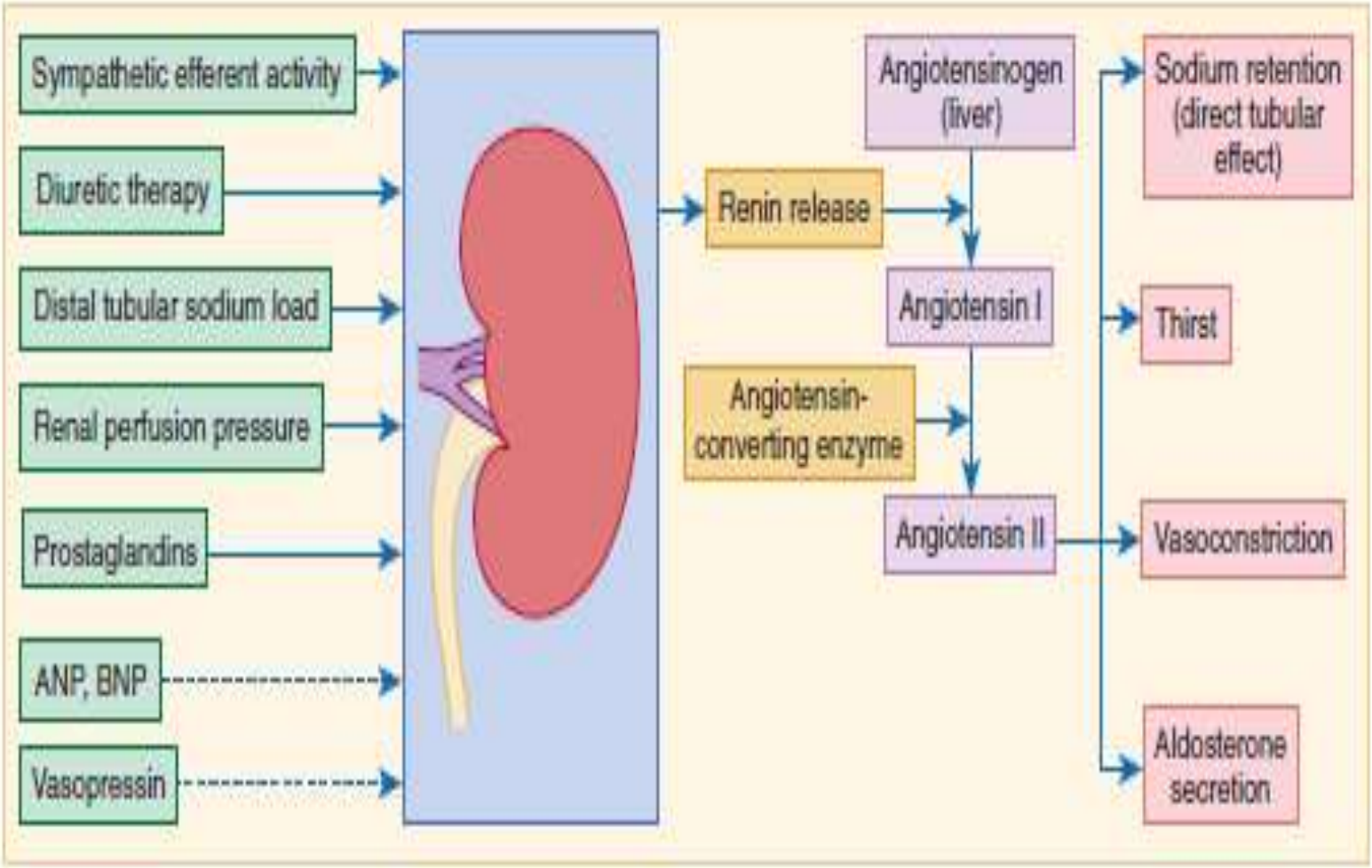


FIGURE 25-3 Activation of the renin-angiotensin system. The renin-angiotensin system is activated in patients with heart failure. The major site of release of circulating renin is the juxtaglomerular apparatus of the kidney, where multiple stimuli may contribute to renal release of renin into the systemic circulation, including renal sympathetic efferent activity, decreased distal sodium delivery, reduced renal perfusion pressure, and diuretic therapy. Natriuretic peptides (ANP, BNP) and vasopressin (dashed arrows) may inhibit the release of renin. Renin enzymatically cleaves angiotensinogen to form angiotensin II from angiotensin I. Angiotensin II is a potent vasoconstrictor and promotes sodium resorption by increasing aldosterone secretion and by a direct effect on the tubules. Angiotensin II also stimulates water intake by directly acting on the thirst center. *(From Nohria A, Cusco JA, Creager MA: Neurohormonal, renal and vascular adjustments in heart failure. In Colucci WS [ed]: Atlas of Heart Failure. 4th ed. Philadelphia, Current Medicine, 2005, p 107.)*

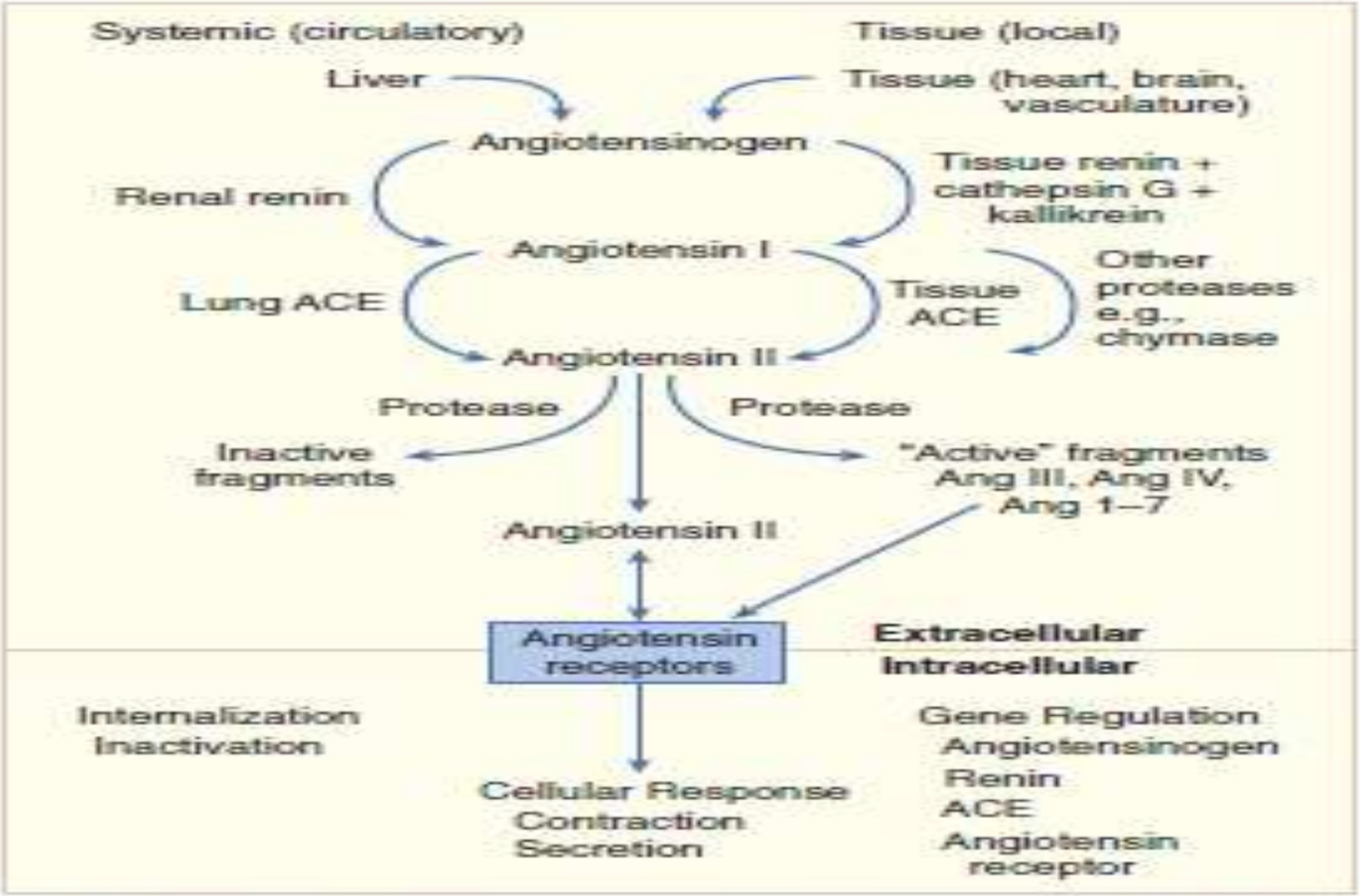


FIGURE 25-4 The systemic and tissue components of the renin-angiotensin system. Several tissues, including myocardium, vasculature, kidney, and brain, have the capacity to generate angiotensin II independent of the circulating renin-angiotensin system. Angiotensin II produced at the tissue level may play an important role in the pathophysiology of HF. ACE = angiotensin-converting enzyme. *(Modified from Timmermans PB, Wong PC, Chiu AT, et al: Angiotensin II receptors and angiotensin II receptor antagonists. Pharmacol Rev 45:205, 1993.)*

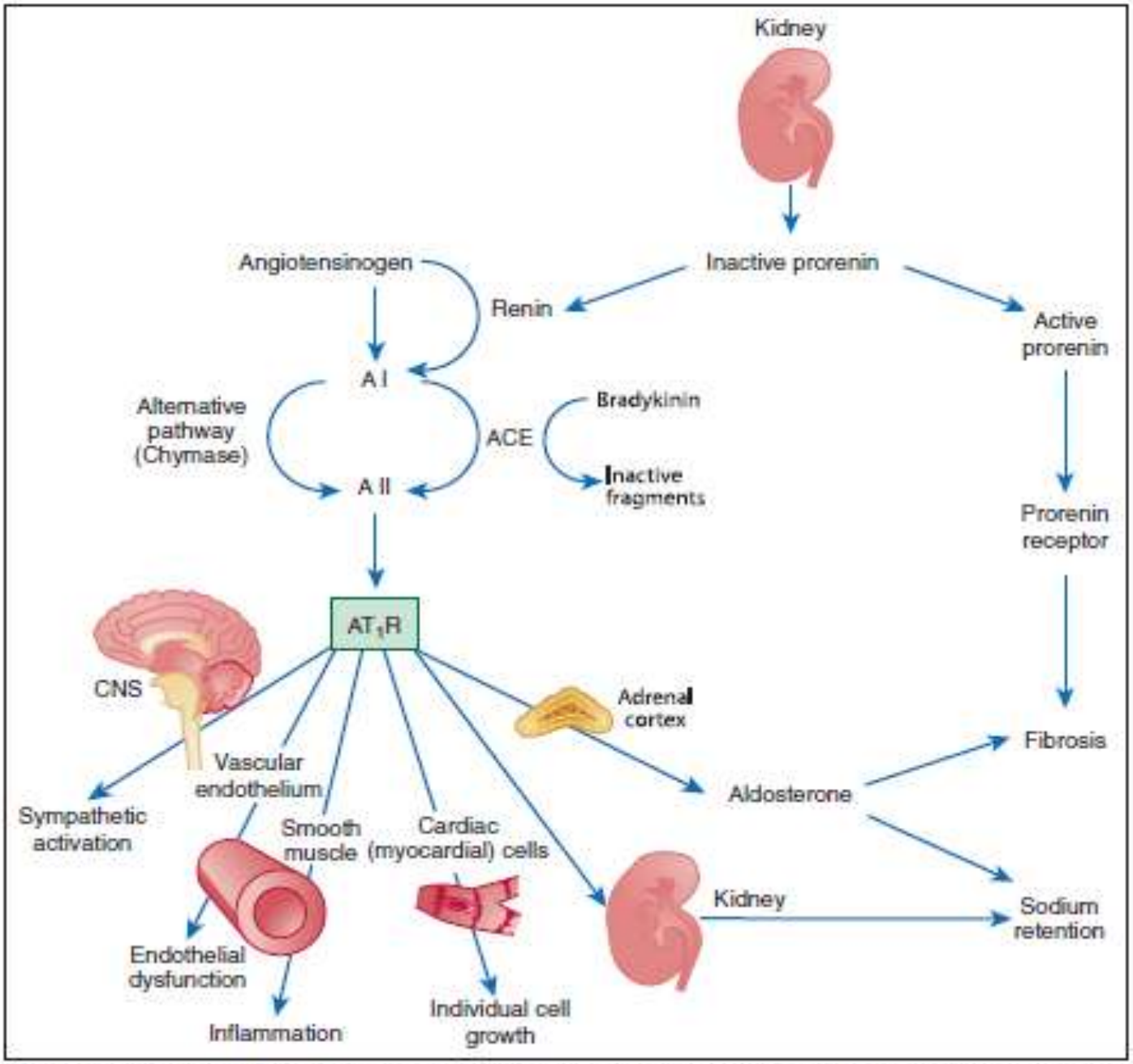


FIGURE 45-8 The renin-angiotensin-aldosterone system. A I = angiotensin I; A II = angiotensin II; ACE = angiotensin-converting enzyme; AT_1R = angiotensin I receptor.

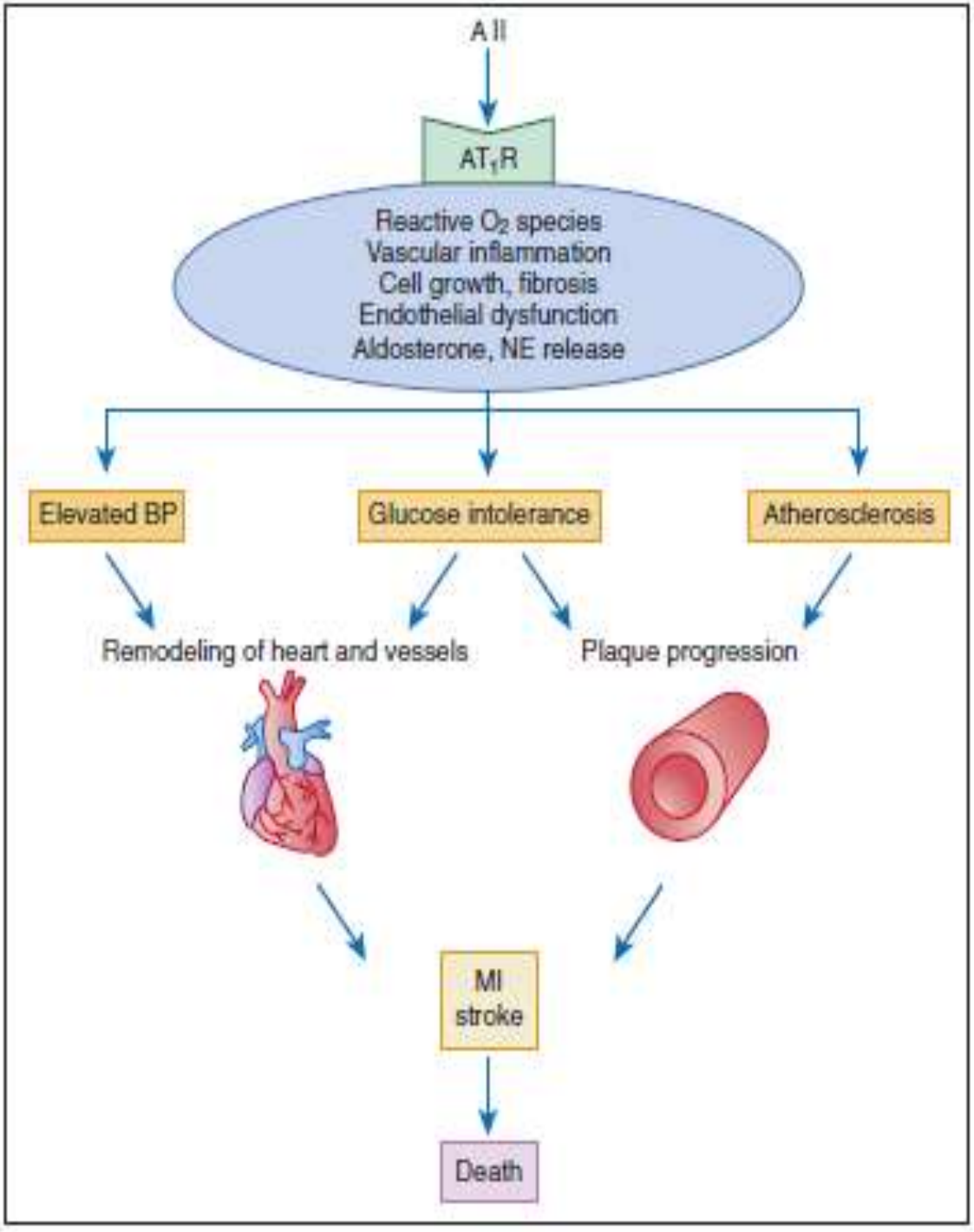


FIGURE 45-9 Schematic representation of the central role of angiotensin 1 receptor (AT_1R)-mediated signaling in cardiovascular disease progression. A II = angiotensin II; MI = myocardial infarction; NE = norepinephrine.

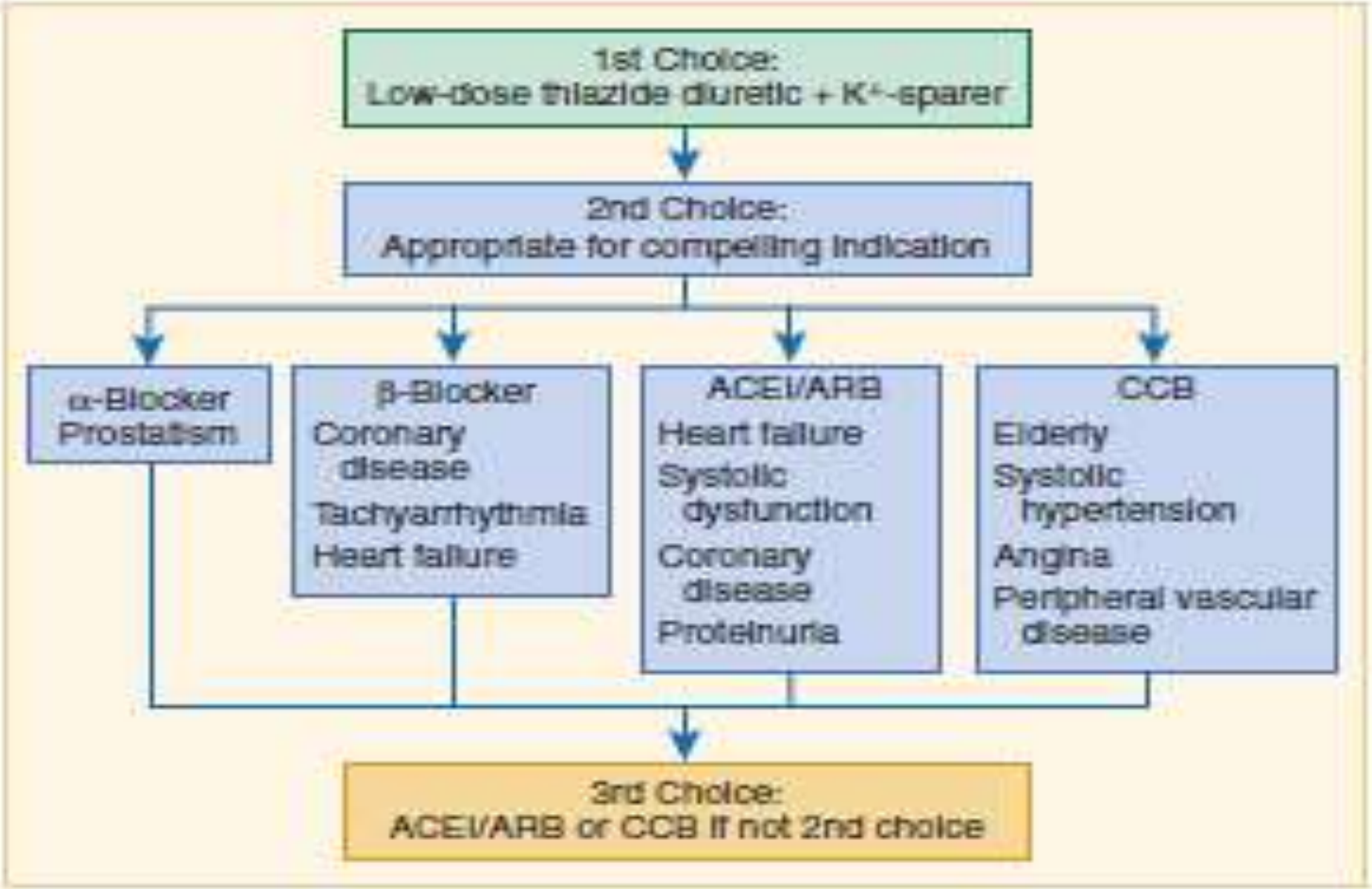


FIGURE 46-6 Algorithm for therapy of hypertension. Increasing evidence favors an aldosterone blocker as the fourth choice and perhaps as the third choice for many patients.

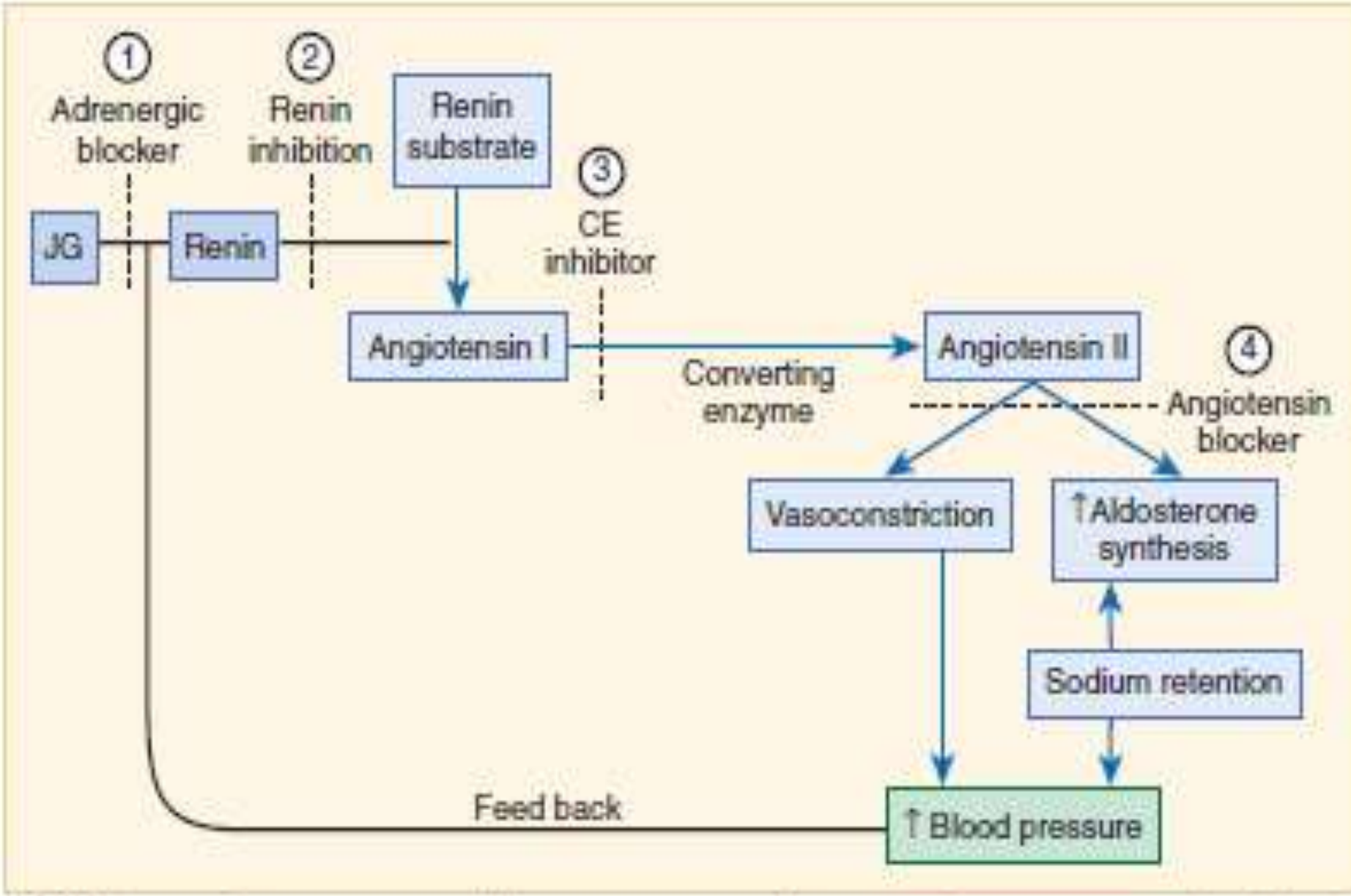
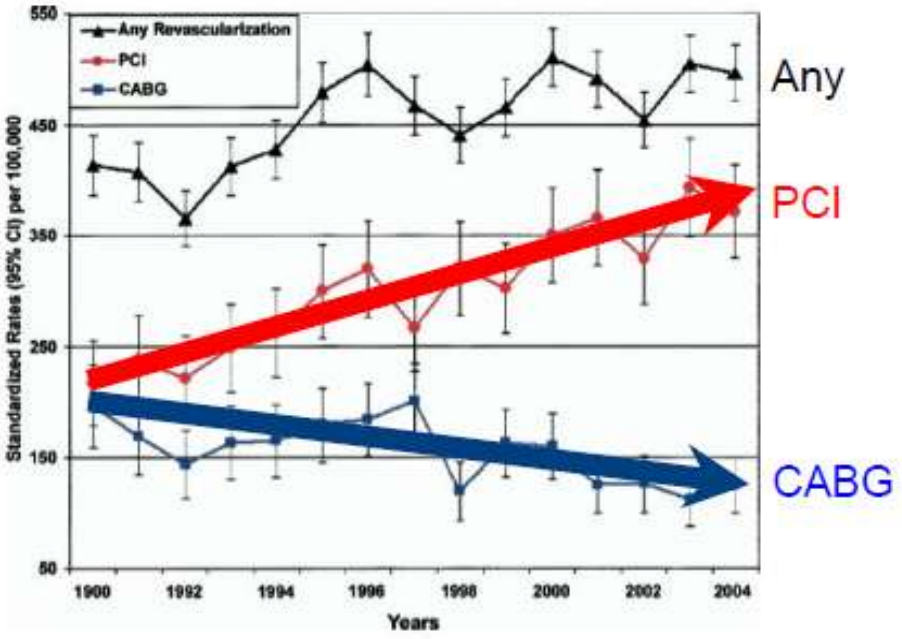


FIGURE 46-10 Renin-angiotensin-aldosterone system and four sites where its activity can be inhibited. CE = converting enzyme; JG = juxtaglomerular cells.

Revascularization Trends

Olmsted County, Minnesota from 1990 - 2004



Y. Gerber et al., J. Am. Coll. Cardiol. 50, 1223 (2007).

Nomenclature

- Contrast nephropathy (CN)
- Contrast induced nephropathy (CIN)
- Contrast medium-induced nephropathy (CIN)
- Contrast induced – acute kidney injury (CI-AKI)

Measuring Renal Function

Serum Creatinine

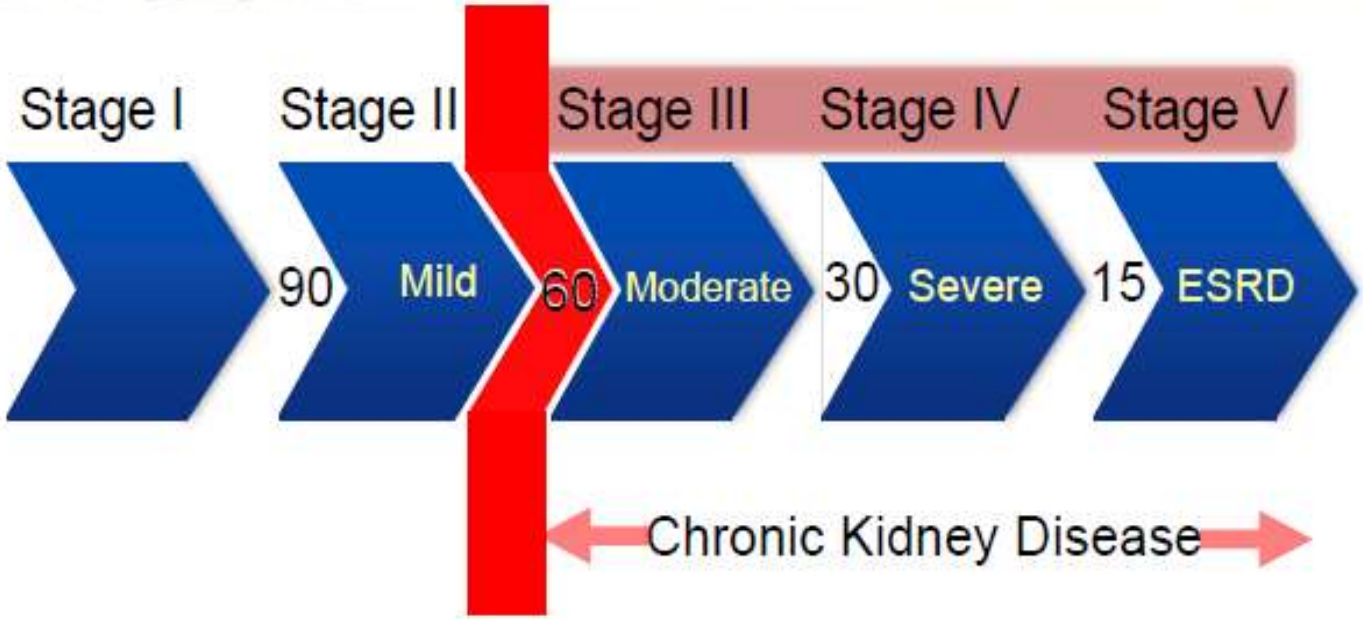
- Easy
- Universal
- No calculation required

Glomerular Filtration Rate

- More accurate
- Adjusted for
  - Age
  - Gender
  - Race
- Needs to be calculated

Classification of Kidney Function

estimated GFR (mL/min/1.73 m^2)



CIN is increased when eGFR < 60. For most RCTs inclusion criteria require eGFR < 60.

Endorsement for eGFR?

eGFR = estimated GFR

"...estimates of GFR are the best overall indices of the level of kidney function."

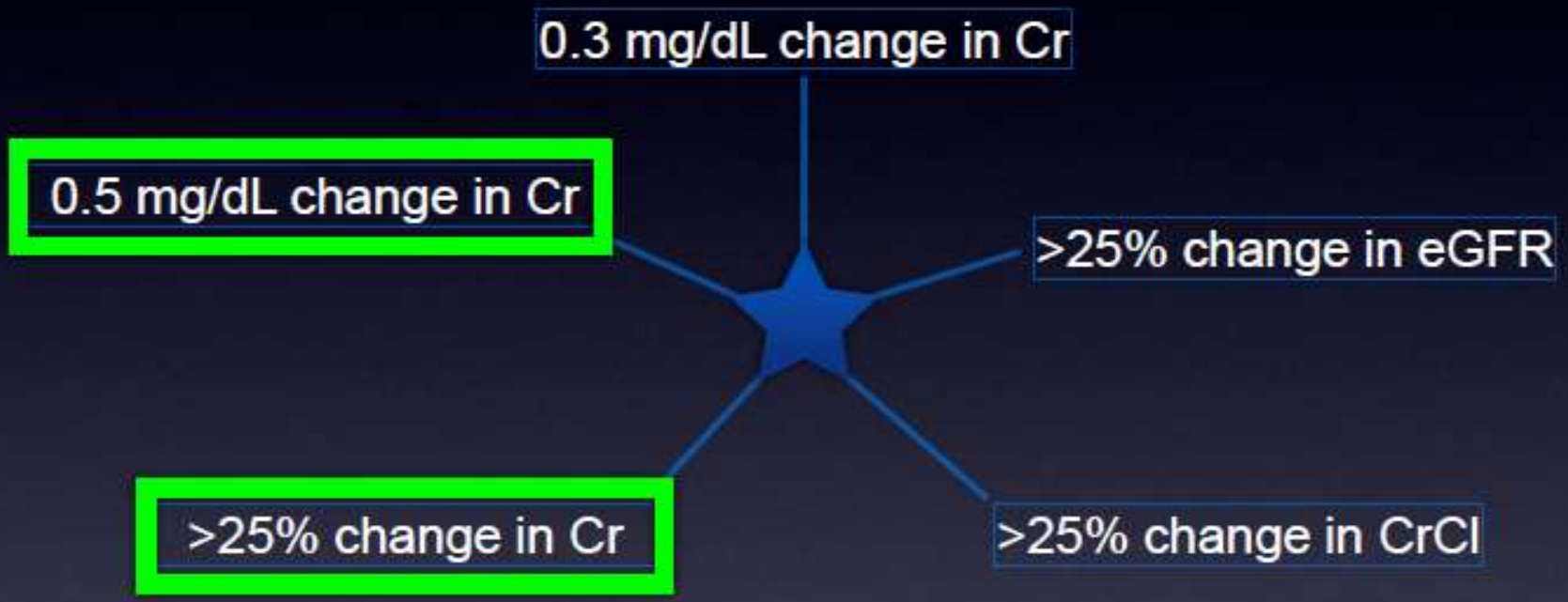
National Kidney Foundation
Kidney Disease Outcomes Quality Initiative
Am J Kidney Dis, 2002

"The risk of contrast-induced acute kidney injury is elevated and of clinical importance in patients with chronic kidney disease, recognized by an eGFR rate < 60."

CIN Consensus Working Panel
McCullough et al. Am J Cardiol, 2006

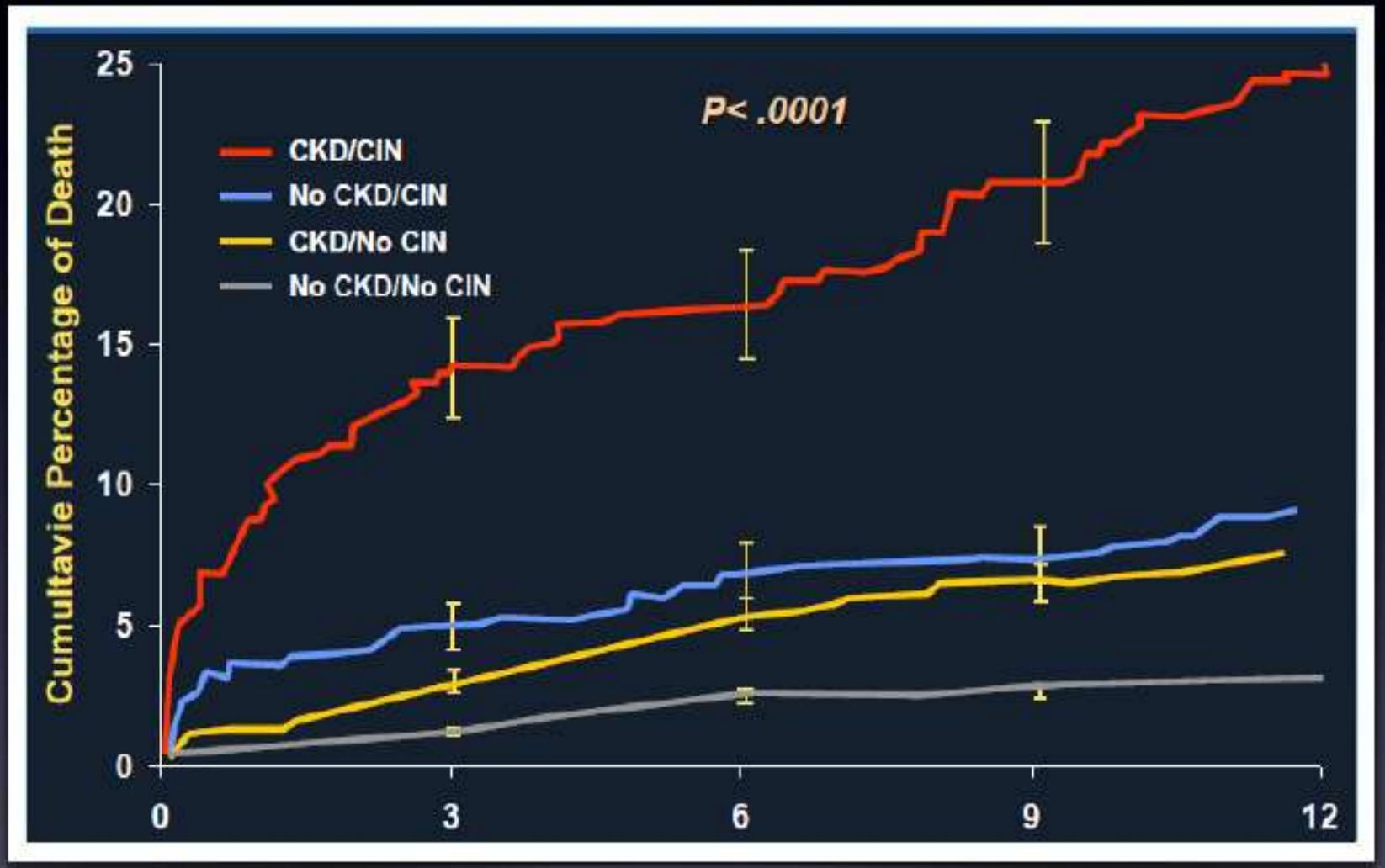
Definitions

Contrast Induced Nephropathy (CIN)



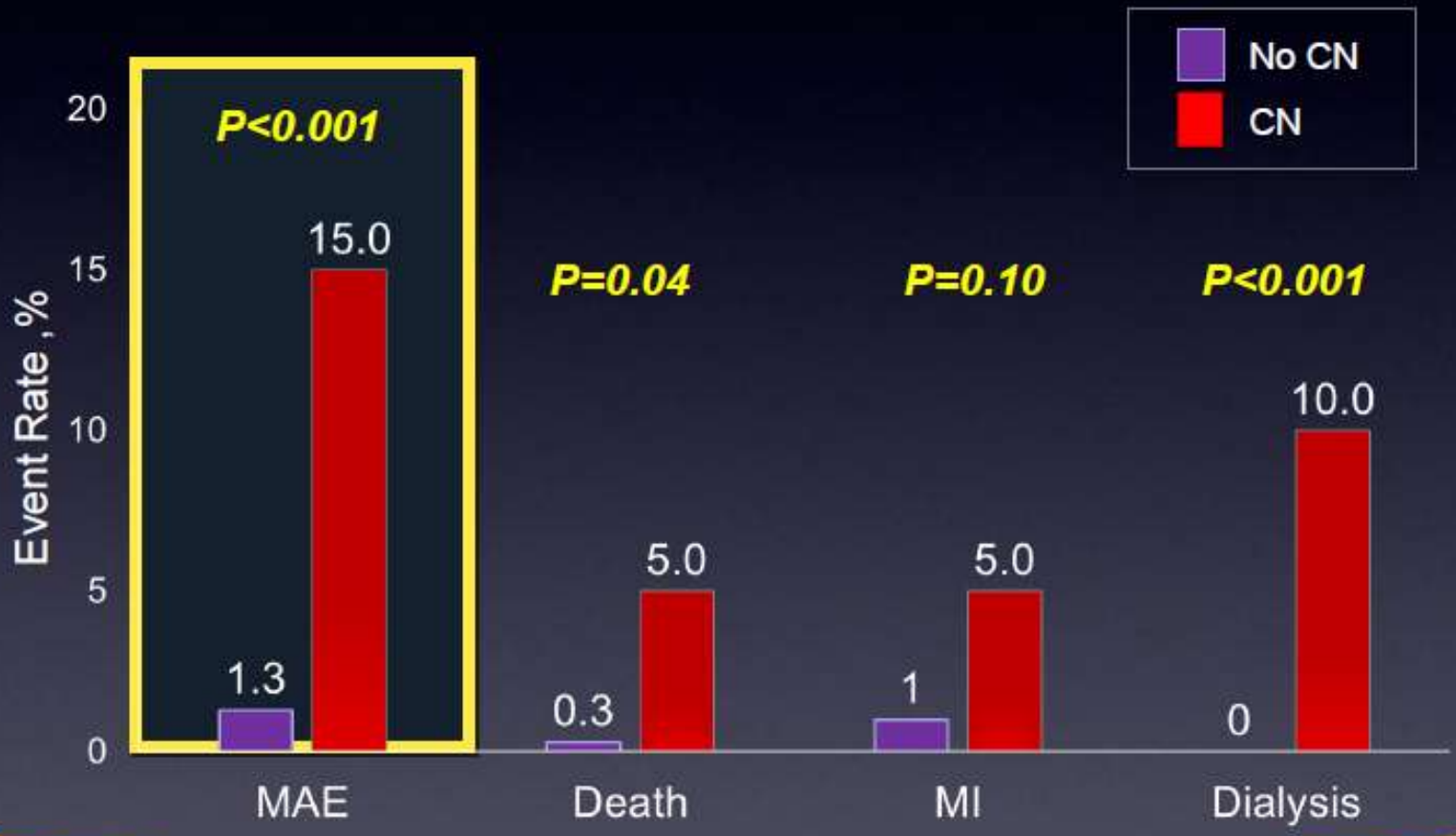
Can be first identified 24-48 hours post-contrast exposure, with creatinine peak 4-7 days later and normalizing within 7 to 10 days in most cases.

Prognostic Significance of CIN



POSEIDON: 30-day MAE

by Contrast Nephropathy (CN) status



KAISER PERMANENTE
Regional Cardiac Cath Lab

Brar et al. TCT 2012

POSEIDON

Quantifying Risk

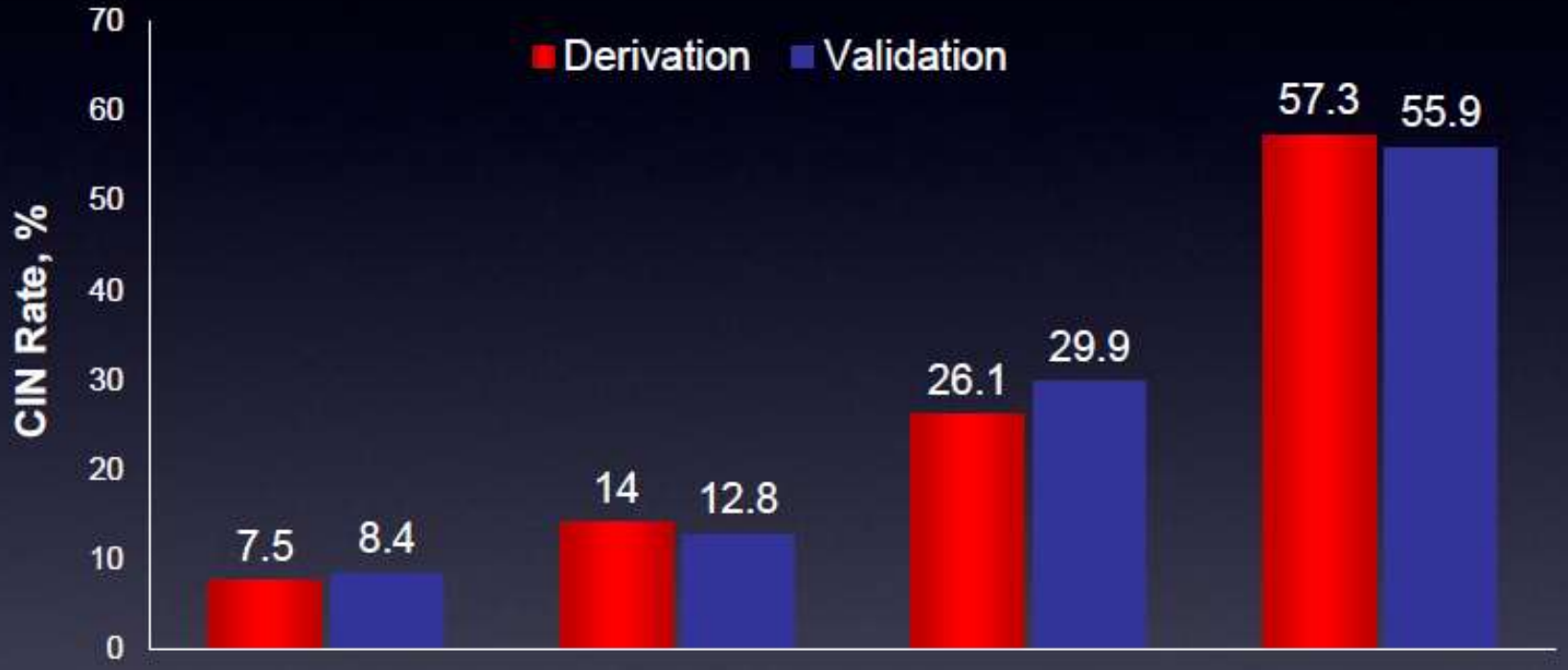
Risk Factors	Integer Score
Hypotension	5
IABP	5
CHF	5
Age > 75 yrs	4
Anemia	3
Diabetes	3
Contrast vol.	1 for each 100 mL
SCr > 1.5 mg/dL	4
or	
eGFR < 60 mL/min/1.73m²	2 for 40-60 4 for 20-40 6 for <20

Risk Score	Risk of CIN	Risk of Dialysis
≤ 5	7.5%	0.04%
6 to 10	14.0%	0.12%
11 to 16	26.1%	1.09%
≥ 16	57.3%	12.6%

Mehran et al. JACC 2004; 44:1393-99

CIN Risk Score

Derivation & Validation



KAISER PERMANENTE
Regional Cardiac Cath Lab

Mehran et al. JACC 2004; 44:1393-99

UCLA
School of Medicine

Prevention

What's Hot & What's Not?

N-acetylcysteine

Sodium Bicarbonate

Hydration

Contrast removal

Contrast type

Possible Therapies

N-acetylcysteine

normal saline

D5 1/2 NS

fenoldapam

diuretics

hemodialysis

cooling

mannitol

ascorbic acid

hemoflitration

CS aspiration

statins

theophylline

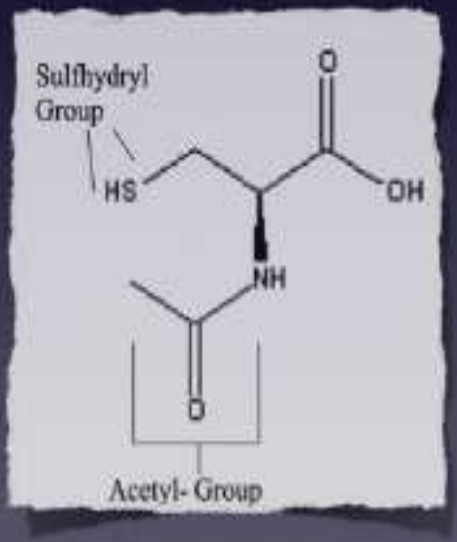
Matched hydration-diuresis

acetazolamide

bicarbonate

N-acetylcysteine

- Acetaminophen overdose
- Mucolytic
- Antioxidant



NAC

Potentially Favorable Effects

- Direct scavenger of free radicals
- Causes vasodilation through NO mediated pathways
- Precursor of glutathione (natural antioxidant)
- Prevent apoptosis & promote cell survival

NAC

Pharmacology & Metabolism

Oral administration

- Bioavailability: approx 4% in the reduced (active) form
- First-pass hepatic metabolism

IV administration

- Reduced form: $t_{1/2}$ of 8-10 minutes.
- Reduced + oxidized: $t_{1/2}$ of ~120 minutes.

NAC

Evidence that NAC is Renoprotective

Cisplatin

No NAC	Cisplatin Induced Nephropathy
50 mg/kg IV	Cisplatin Induced Nephropathy
400 mg/kg PO	Cisplatin Induced Nephropathy
400 mg/kg IV	Protected
50 mg/kg IA	Protected*

KAISER PERMANENTE
Regional Cardiac Cath Lab

Stentstrom et al. J Vasc Interv Radiol 2008; 19:309-318
*Dickey et al. Cancer Chemother Pharmcol 2007

UCLA
School of Medicine

What's the right dose?

There is no reported basis for the currently studied doses except that it was used in earlier phase III trials.

What's the right dose?

A

B

NAC Toxicity

Side Effects of IV N-acetylcysteine

Most Frequent

- rash, urticaria, pruritis

Serious

- angioedema, hypotension, hypertension
- tachyarrhytmia

Other

- decrease in PT

Acetaminophen overdose: 150 mg/kg bolus followed by 50-100 mg/kg IV over 4 to 16hrs. In one series adverse reactions 17%.

Summarizing the Literature

29 trials for renal protection with NAC, 2000-6

Positive n=14

Author	N-Acetylcysteine Dose
Tepel et al (1)	600 mg orally twice daily for 48 h
Diaz-Sandoval et al (9)	600 mg orally twice daily for 48 h
Briguori et al (7)	600 mg orally twice daily for 48 h
Shyu et al (47)	400 mg orally twice daily for 48 h
Kay et al (40)	600 mg orally twice daily for 48 h
Baker et al (5)	150 mg/kg IV before and 50 mg/kg IV after
Tadros et al (72)	600 mg orally twice daily 3 doses
MacNeill et al (53)	600 mg orally twice daily 5 doses
Efrati et al (54)	1,000 mg orally twice daily for 48 h
Briguori et al (44)	Single dose, 600 mg orally twice daily for 48 h; double dose, 1,200 mg orally twice daily for 48 h
Ochoa et al (55)	1,000 mg orally 1 h prior and 4 h after
Miner et al (56)	2,000 mg orally twice daily, 3 doses; if randomized 1 day earlier or two doses if same day
Drager et al (57)	600 mg orally twice daily for 4 days (first dose 48 h before procedure)
Marenzi et al (4)	600 mg IV before, 600 mg orally twice daily for 48 h 1,200 mg IV before and 1,200 mg orally twice daily for 48 h

Negative n=15

Allaqaband et al (58)	600 mg orally twice daily for 48 h
Durham et al (59)	1,200 mg orally 1 h before and repeat 3 h after
Goldenberg et al (60)	600 mg orally three times daily for 48 h
Oldemeyer et al (51)	1,500 mg orally twice daily for 48 h
Boccalandro et al (45)	600 mg orally twice daily for 48 h
Kefer et al (61)	1,200 mg IV 12 h before, repeat with contrast agent
Webb et al (48)	500 mg IV 1 h before
Fung et al (62)	400 mg orally twice daily for 48 h
Rashid et al (49)	1,000 mg IV before, 1000 mg IV after
Gomes et al (41)	600 mg orally twice daily for 48 h
Gulel et al (13)	600 mg orally twice daily for 48 h
Azmus et al (46)	600 mg orally twice daily for 48 h and 1 day after
Kotlyar et al (50)*	300 mg IV 1–2 h before and 2–4 h after 600 mg IV 1–2 h before and 2–4 h after
Coyle et al (42)	600 mg orally twice daily for 48 h
Carbonell et al (43)	600 mg orally twice daily for 48 h

KAISER PERMANENTE
Regional Cardiac Cath Lab

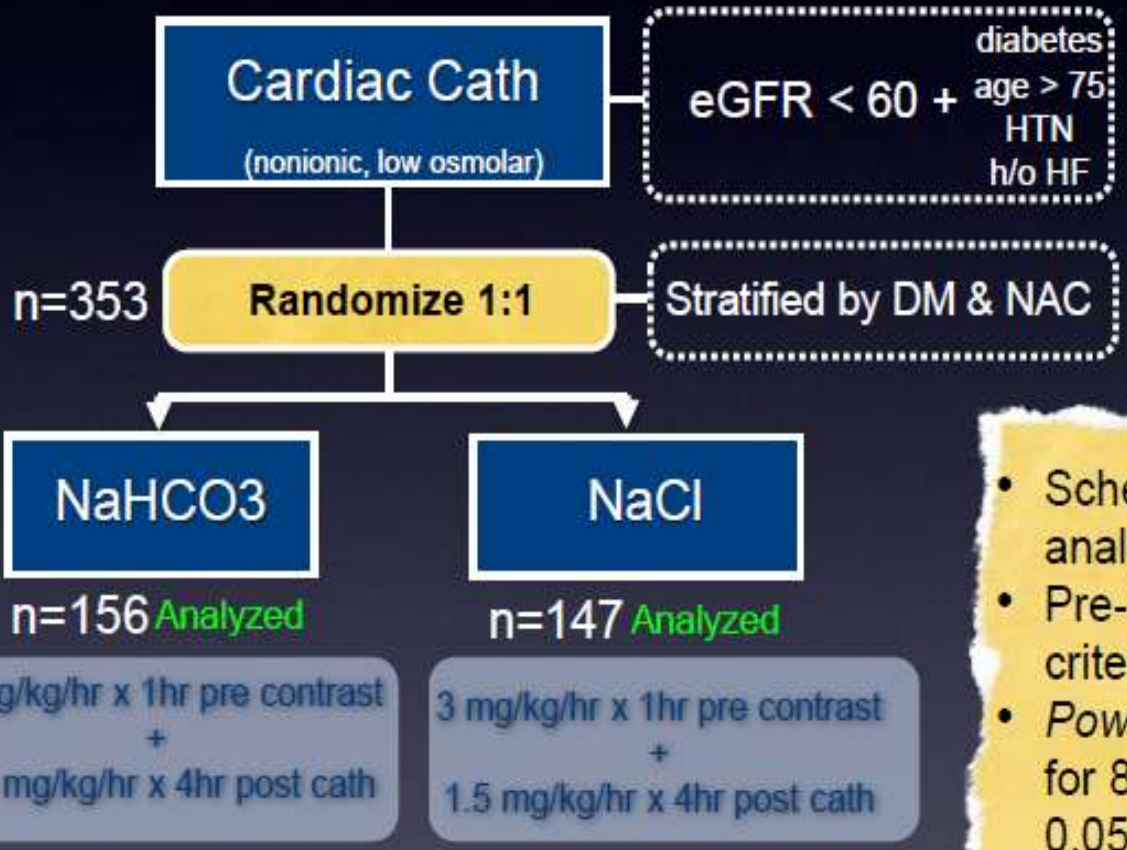
Stentstrom et al. J Vasc Interv Radiol 2008; 19:309-318

UCLA
School of Medicine

Sodium Bicarbonate

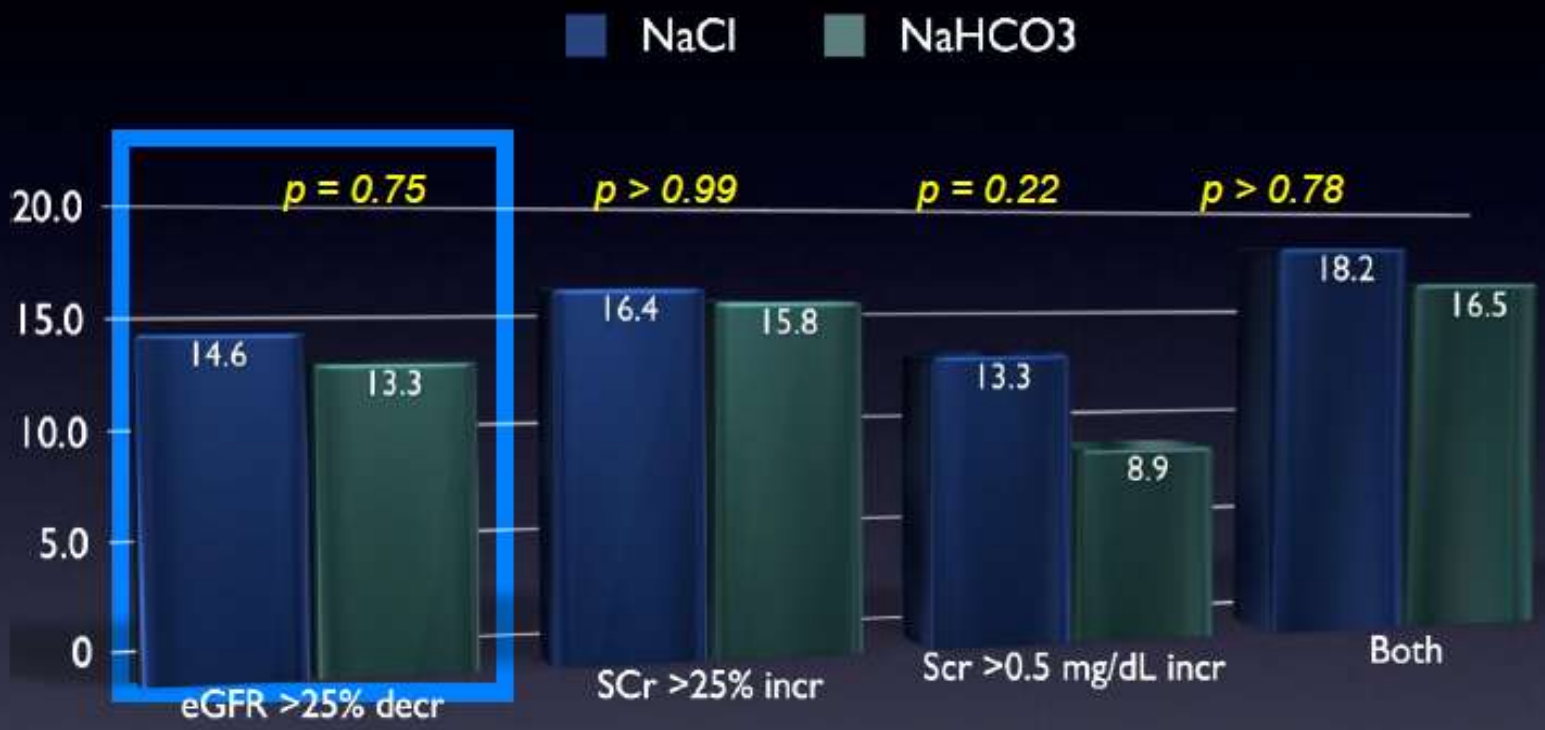
MEENA Trial

Randomized Comparison Between Sodium Bicarbonate & Chloride Among Patients Undergoing Cath



- Scheduled interim analyses
- Pre-specified stopping criteria
- *Power calc* = 290 pts for 80% power, alpha 0.05.

CIN Incidence



In patients undergoing cardiac cath periprocedural hydration with sodium bicarbonate or sodium chloride resulted in similar rates of CIN

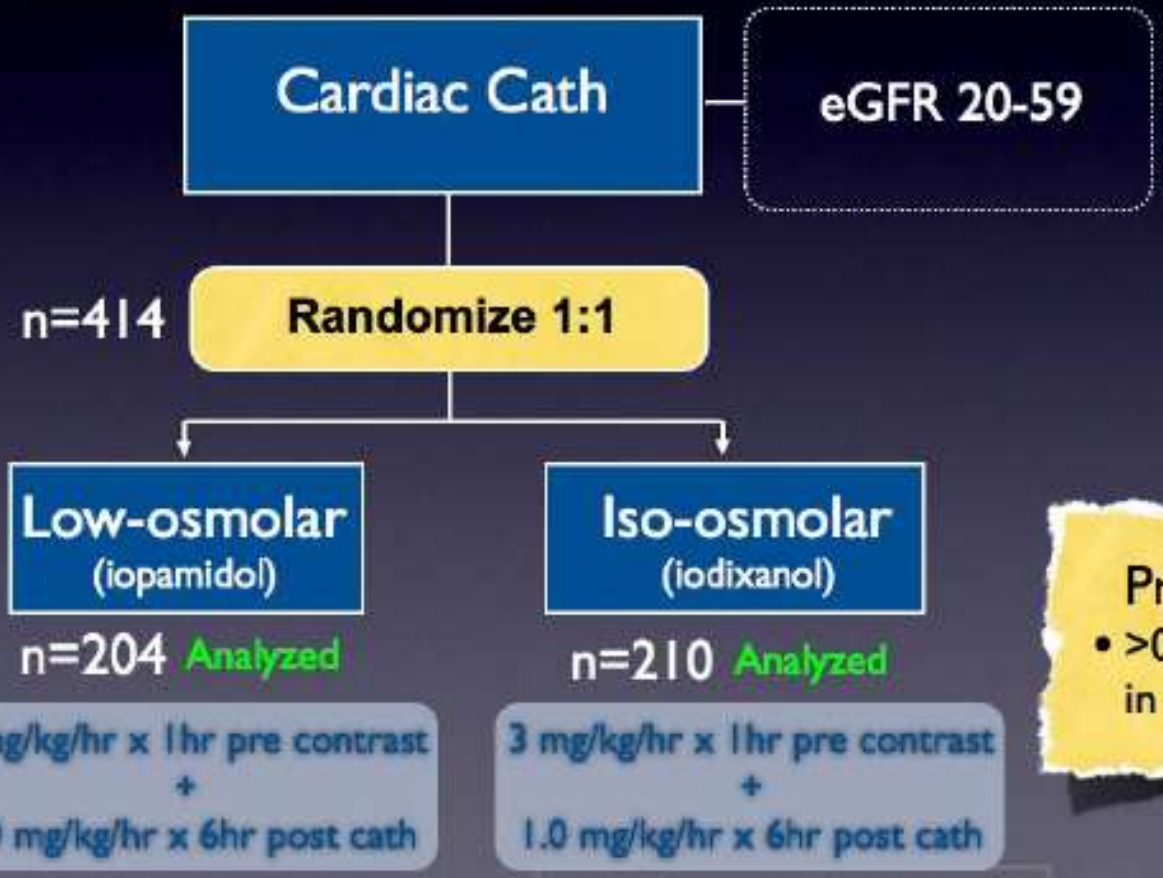
Brar et al. JAMA, 2008

Contrast Media

Iso-osmolar vs. Low-osmolar

CARE Trial

Randomized Comparison Between Iso-osmolar & Low-osmolar Contrast Media in Patients Undergoing Cath



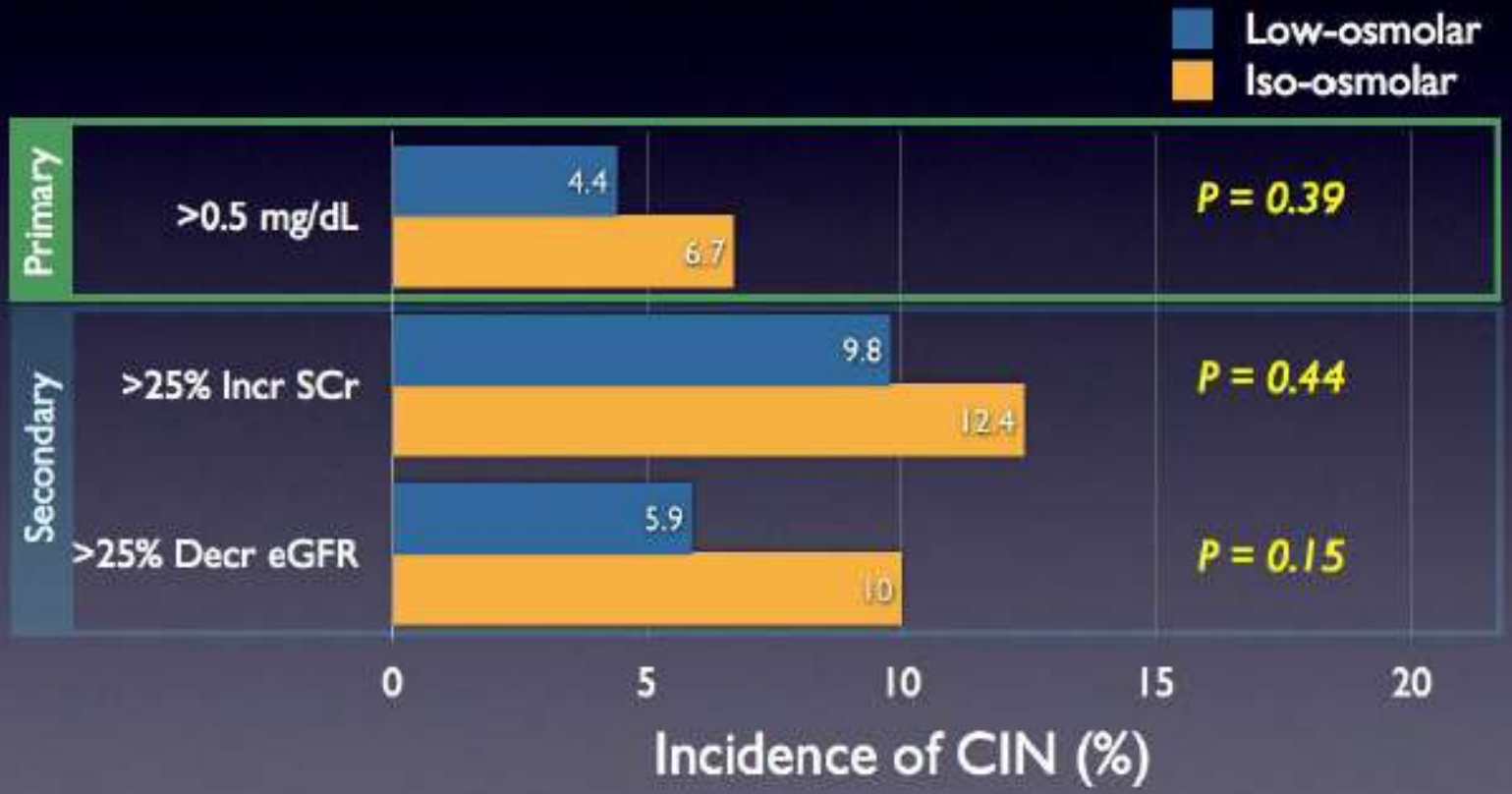
Primary endpoint:

- >0.5 mg/dL increase in serum Cr

Solomon et al. Circulation 2007

CARE Trial

Results: Iso-osmolar vs. Low-osmolar Contrast Media



Solomon et al. Circulation 2007

Hydration

Contrast Nephropathy

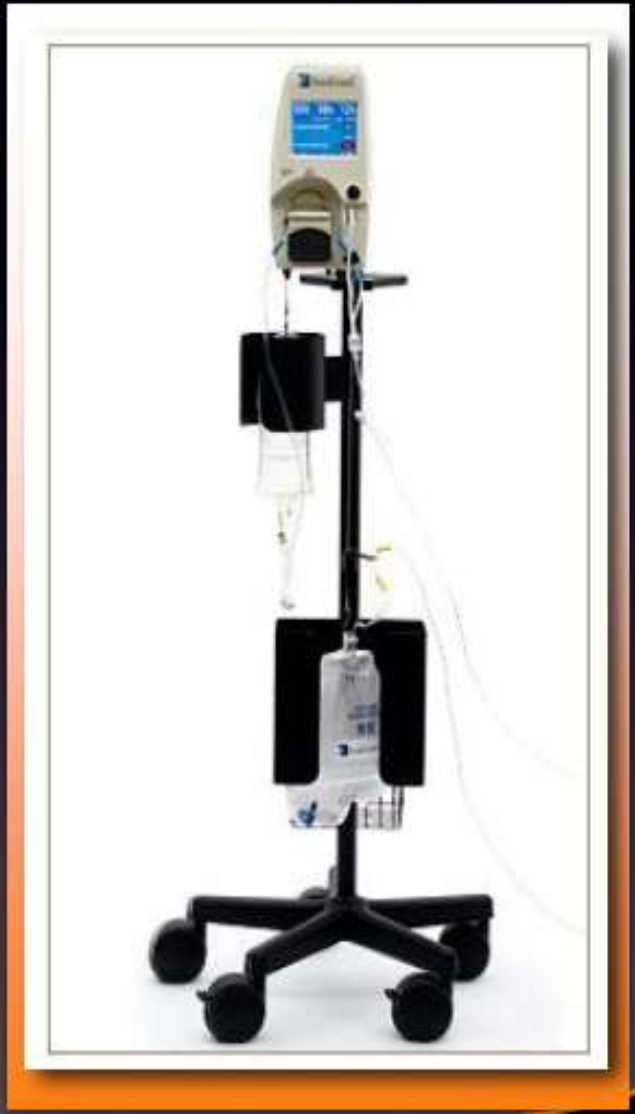
Unknowns Regarding Hydration

Hydration, with normal saline (0.9% saline), remains the cornerstone of CN prevention, yet important questions remain:

- Rate of hydration?
- Duration of hydration?
- Uniform rate for everyone or can the rate be optimized to the patients needs?

Renal Guard

- Diuretics alone increase rate of CIN
- Renal Guard system:
  - System designed to preserve theoretical benefits of diuretics (increase urine flow rate) while minimizing risks.
  - Designed to automatically match i.v. fluid replacement with urine volume in real-time.
  - Furosemide induced forced diuresis
- Possible effects:
  - Dilute contrast agent in renal tubules
  - Reduce kidneys exposure time to contrast
  - Decrease risk of over- or under-hydration.



Contrast Mitigation & Removal

Preserve Trial

- Catheter placed in the coronary sinus
- Partial occlusion
- Active aspiration from the coronary sinus during contrast injection
- Coupled with injector to minimize contrast reflux from coronary

Alternatives to Iodinated Contrast Media

- CO_2
- IVUS
- OCT
- Ultrasound

Getting by Without Contrast

The Future or Science Fiction?

Contrast Induced Nephropathy & Radiation Safety

Fellows Course 2013

Somjot S. Brar, MD, MPH

Director of Vascular Medicine
Interventional Cardiologist & Vascular Specialist
Kaiser Permanente, Los Angeles
Assistant Clinical Professor of Medicine, UCLA

Conclusions

Contrast Nephropathy

- CI-AKI (CIN) remains a frequent source of acute renal failure and is associated with increased morbidity and mortality.
- Multiple factors predispose patients to CI-AKI and validated risk models are available.
- Preventive measures need to be taken pre-, during-, and post-procedure.

Conclusions

Contrast Nephropathy

- Clinical trial data can be confusing and conflicting. Take care in interpreting the literature.
- Limit contrast and hydrate
- D/C nephrotoxic drugs
- No role for N-acetylcysteine or sodium bicarbonate (in the absence of new data)
- Low-osmolar agents likely equivalent to iso-osmolar in terms of CIN risk.


THANK YOU
مركز تقنية الاتصالات والمعلومات - جامعة المنصورة